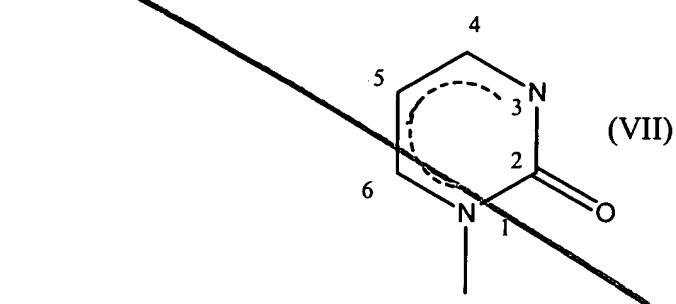


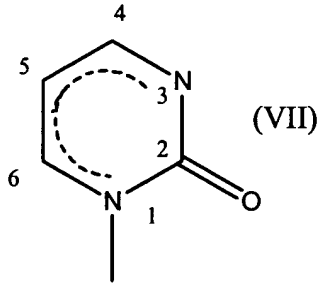
(VII)

substituted at position 4 with =O and substituted at position 5 with CH_3.

REMARKS

I. Status of the Claims

Formula VII of Claims 56 and 95 have been amended in an effort to better illustrate Applicants' claimed invention. Specifically, Formula VII has been amended to illustrate by means of a dotted line (a notation understood by one of skill in the art) the ability of a pair of electrons to shift between any two adjacent atoms and thereby allow the compound to retain its aromatic character:



(VII)

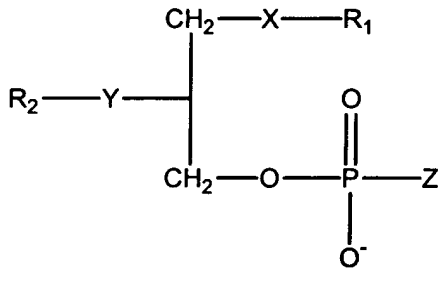
Support for the amendment to the claims can be found in the claims as originally filed and throughout the specification, including page 12, lns. 20-29. No new matter has been added by the present amendment.

Claim 56 has also been amended and claims 103-109 have been added to define the viral infections combated by the compound of Formula III. Support for this amendment can be found in the specification on page 14, line 20 to page 15, line 8 and the Declaration Under §1.132 of Louis S. Kucera submitted herewith. Upon entry of these amendments, Claims 56-71, 95-96 and 103-109 will be pending.

II. Rejection of Claims 56-71, 95, and 96 under 35 U.S.C. §112, second paragraph

Claims 56-71, 95, and 96 stand rejected under 35 U.S.C. §112, second paragraph as set forth in paragraphs d) and f) on pages 2-3 of the Office Action (Paper No. 17) mailed on May 23, 2001 and as restated on pages 2-4 of this Office Action (Paper No. 19). Applicants respectfully traverse this rejection.

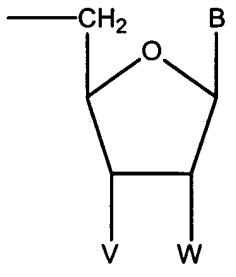
Applicants' claimed invention is drawn to a compound of Formula III (Claims 95-96):



(III)

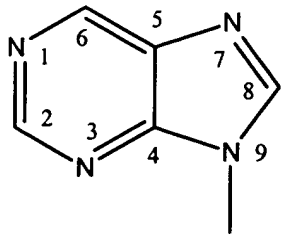
and a method of combating a viral infection in a subject in need of such treatment comprising administering to the subject an effective infection-combating amount of a compound of Formula III (Claims 56-71).

In Formula III, as set forth above, Z is a moiety of Formula V:

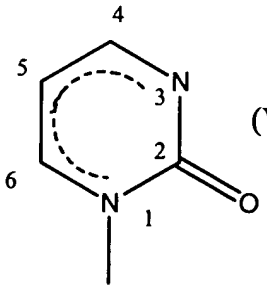


(V)

where B is either a purinyl moiety of Formula VI or a pyrimidinyl moiety of Formula VII (as amended):



(VI)



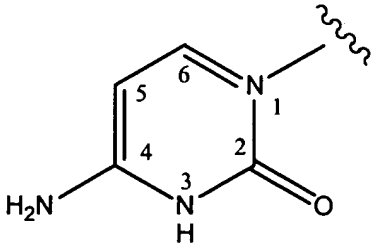
(VII)

See claims 56 and 95. Also, as set forth in claims 56 and 95, in Formula VII, the 4-position can be substituted with a =O or $-NH_2$ groups and optionally substituted at the 5-position with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.

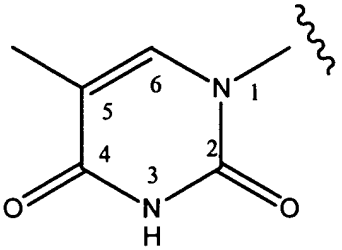
As defined in the specification on page 12, lns. 21-27:

> "...a pyrimidinyl moiety comprises a six-membered aromatic ring having the molecular structure illustrated in Formula VII. Those skilled in [the] art will appreciate that the double bonds illustrated in Formula VII are included therein to represent that the moieties of Formula VII have aromatic character, and that these double bonds may shift for certain substituents, in particular for =O and $-NH_2$ at positions 2 and 4, in order for the moiety to retain its aromatic character."

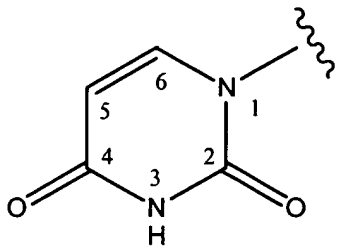
Examples of preferred "B" moieties of Formula VII include cytosine, thymine, uracil and 5-fluorouracil. Specification, page 12, lns. 27-29. Thus Formula VII is meant to include the pyrimidines of cytosine, thymine, uracil and 5-fluorouracil which have the following structures:

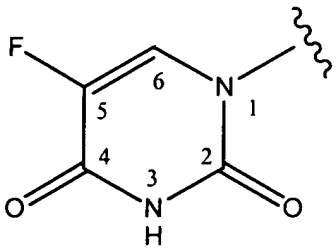


cytosine ;



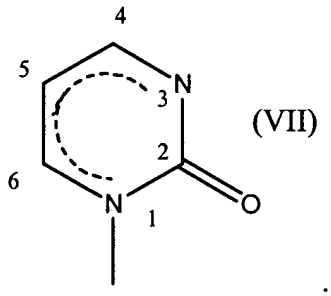
thymine ;



uracil ; and  5-fluorouracil .

As exemplified by cytosine, the double bond between positions 5 and 6 of formula (VII) "...may shift for certain substituents, in particular for =O and -NH_2 at positions 2 and 4, in order for the moiety to retain its aromatic character." More specifically, when B is cytosine, the 4 position is substituted with a -NH_2 moiety and the double bond shifts from the 5-6 position to the 4-5 position while the lone pair on the nitrogen at the 1-position donates into the ring to form a double bond between the 1 and 6 positions. As a result, the compound retains its aromatic character.

Thus, solely to better clarify Applicants' claimed invention, the structure of formula (VII) of independent claims 56 and 95 and the specification on pages 5 and 6 has been amended to read as follows:



(VII)

As would be understood by one of skill in the art, the dotted line represents the ability of a pair of electrons to shift between positions 1, 6, 5, 4 and 3 in order for the compound to retain its aromatic character. Also as would be understood by one of skill in the art, the lone pair of electrons on the nitrogen at either the 1- and/or 3- position can be donated into the ring in order for the ring to retain its aromatic character. For example, the lone pair on the nitrogen at the 3-position could be donated to the ring to isomerize with the alpha-carbonyl group at either the 2-

or 4-position to form the enol. Alternatively, if the 4-position is substituted with a $-NH_2$ group, the lone pair on the nitrogen at the 3-position could be donated into the ring to form a double bond between the 3-4 position. As a result of the amendment to Formula VII, there would be no need to a hydrogen to the nitrogen at the 3-position since to do so would create a quaternary ammonium at the 3-position. In the event that no double bond exists between the 3-4 position, one of skill in the art would understand that the 3-position nitrogen would have a hydrogen. In view of the amendments to the claims, Applicants respectfully request this rejection be withdrawn.

III. Rejection of Claim 68 under 35 U.S.C. 112, second paragraph

Claim 68 stands rejected under 35 U.S.C. §112, second paragraph as set forth in paragraph f) on pages 3-4 of the Office Action (Paper No. 17) mailed on May 23, 2001 and as restated on pages 3-4 of this Office Action (Paper No. 19). Applicants respectfully traverse this rejection for the reasons set forth above in Section II. Applicants respectfully request this rejection be withdrawn.

IV. Rejection of Claims 56-71 and 96 under 35 U.S.C. 112, first paragraph

Claims 56-71 and 96 stand rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

As amended, Applicant's claimed invention is drawn to a method of combating a viral infection, wherein the viral infection is a virus selected from the group consisting of HIV-1, HBV, herpes virus, influenza, respiratory syncytial virus, mumps, measles, and parainfluenza virus.

With respect to these viruses, the specification describes how the Z moiety of Formula III has demonstrated anti-viral activity by itself and its conjugation to the remainder of the molecule of Formula III provides multiple active sites for viral inhibition. Specification, page 11, lns. 4-7 and page 12, lns. 3-6. The specification also sets forth the efficacy of the

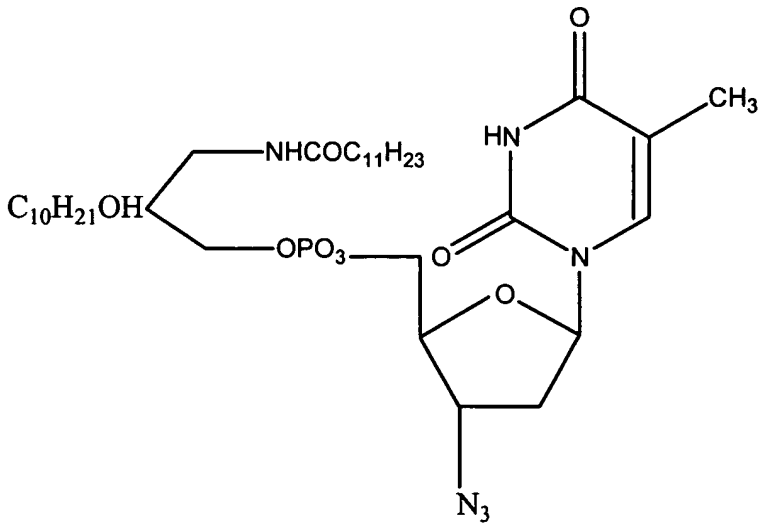
compounds of Formula III in combating viral infection. *See* Specification, page 14, line 20 through page 15, line 8. The specific experimentation for Formula III compounds against HIV-1 activity is provided in the Declaration of Kucera a submitted simultaneously herewith.

The specification still further provides preferred dosage ranges for compounds of Formula III. Specification, page 18, lns. 14-17. However, as would be recognized by one of skill in the art, an effective amount of a compound Formula III administered to combat viral infections would vary based on the subject suffering from the viral infection, the severity of the condition and the nature of the particular active compounds being used. Specification, page 15, lns. 15-17 and lns. 26-29.

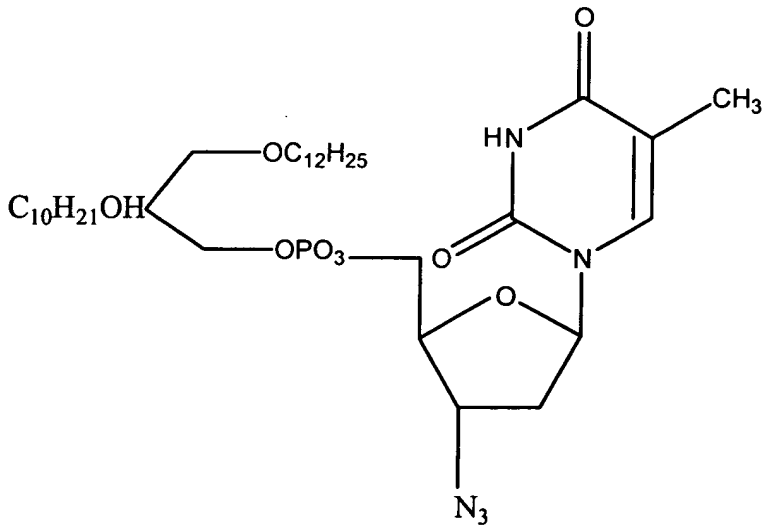
In regard to Claim 96, compounds of Formula III are phosphite anion derivatives including their pharmaceutical salts. The formation and use of such anions and pharmaceutical salts are clearly enabled by the specification.

The specification recites as an exemplary preferred compound of Formula III, 3'-azido-3'-deoxy-5'-(3-dodecanamido-2-decyloxypropyl)-phosphothymidine. Specification, page 13, lns. 1-2. Examples 5 and 6 found on pages 21-23 of the specification illustrate how to make such a compound of Formula III. The structures of Formula III compounds are as follows:

3'-azido-3'-deoxy-5'-(3-dodecanamido-2-decyloxypropyl)-phosphothymidine



3'-azido-3'-deoxy-5'-(dodecyoxy-2-decyloxypropyl)-phosphothymidine



One of skill in the art would understand that a non-ionic form of a compound of Formula III can exist in equilibrium with its ionic form as in, for example, a solution. Furthermore, as set forth in the specification on page 7, lns. 9-22:

> [t]he term 'pharmaceutical salt' refers to a salt that retains the desired biological activity of the parent compound and does not impart undesired toxicological effects thereto. Examples of such salts are (a) salts formed with cations such as sodium, potassium, NH_4^+, magnesium, calcium polyamines,...; (b) acid addition salts formed with inorganic acids...; (c) salts formed with organic acids...; and (d) salts formed from elemental anions....

Such salt formation would be understood by one of skill in the art. Thus, the specification allows one of skill in the art to make a compound of Formula III, including its pharmaceutical salt for use in the claimed method without undue experimentation.

In view of the foregoing remarks and amendment, Claims 56-71 and 96 are fully enabled by the specification and Declaration of Kucera such that one of skill in the art would be able to make and use Applicants' claimed invention without undue experimentation. Applicants respectfully request this rejection be withdrawn.

VI. Conclusion

Applicants respectfully request reconsideration of the subject application in view of the above amendments and remarks. The subject application is now in condition for allowance and early notice to that effect is respectfully solicited.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

By: _____
Kim R. Jessum
Reg. No. 43,694

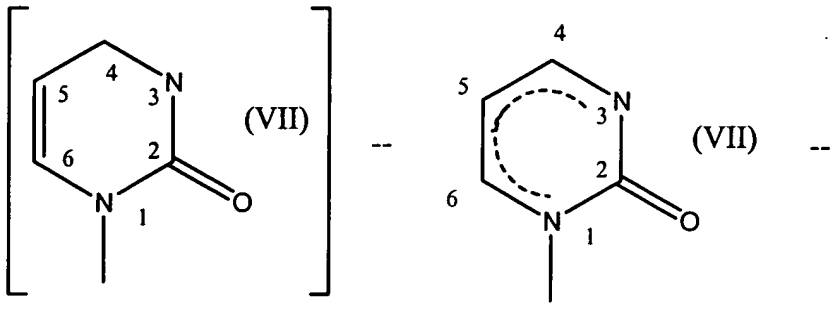
Dated: April 30, 2002
CUSTOMER NO. 028977
MORGAN, LEWIS & BOCKIUS LLP
1701 Market Street
Philadelphia, PA 19103-2921
(215) 963-5000

MARKED UP VERSION

In the Specification :

Please amend page 5, lines 12-21 as follows:

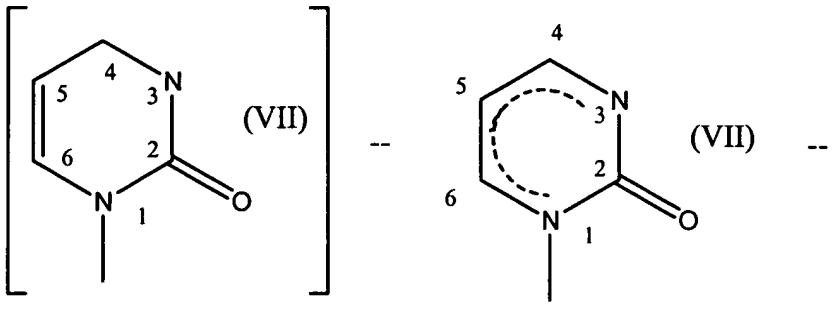
B is a pyrimidinyl moiety of Formula VII



substituted at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.

Please amend page 6, lines 26-page 7, line 3 as follows:

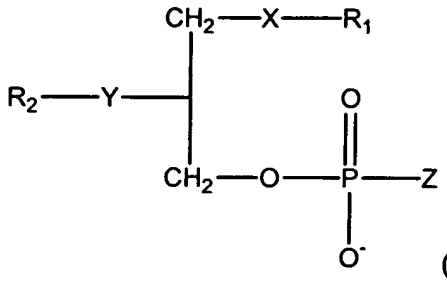
B is a pyrimidinyl moiety of Formula VII



substituted at position 4 with =0 or NH2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.

In the Claims:

56. (Twice Amended) A method of combating a viral infection in a subject in need of such treatment, wherein the viral infection comprises a virus selected from the group consisting of HIV-1, HBV, herpes virus, influenza, respiratory syncytial virus, mumps, measles, and parainfluenza virus, the method comprising administering to said subject an effective infection-combating amount of a compound of Formula III



(III)

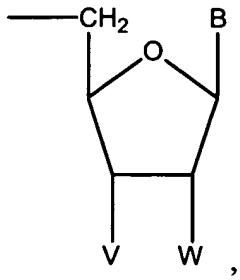
wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; and

Z is a moiety of the Formula V,



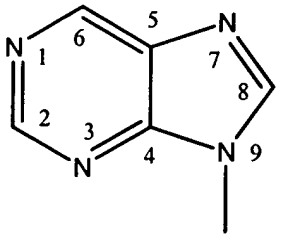
, (V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

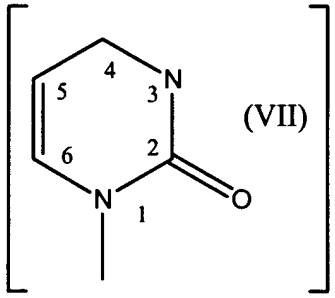
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with -OH, -SH, $-NH_2$ or halogen, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII



(VII)

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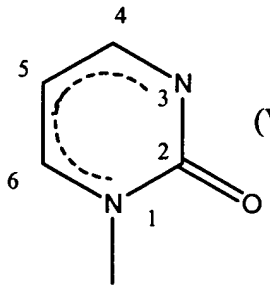

(VII)

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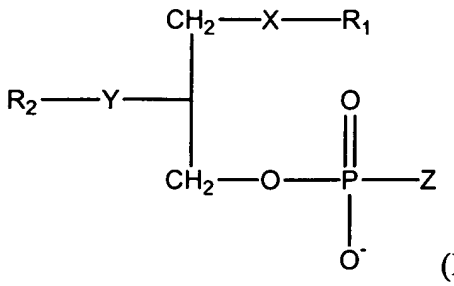
substituted at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen;

or a pharmaceutical salt thereof.

95. (Twice Amended) A compound of Formula III



(III)

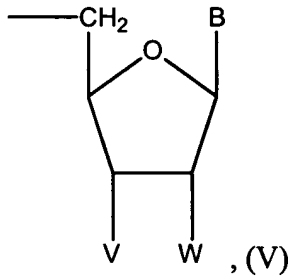
wherein: R_1 is a branched or unbranched, saturated or unsaturated C_6 to C_{18} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

X is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3;

R_2 is a branched or unbranched, saturated or unsaturated C_6 to C_{14} alkyl group optionally substituted from 1 to 5 times with -OH, -COOH, oxo, amine, or substituted or unsubstituted aromatic;

Y is selected from the group consisting of NHCO, CH_3NCO, CONH, $CONCH_3$, S, SO, SO_2, O, NH, and NCH_3; and

Z is a moiety of the Formula V,



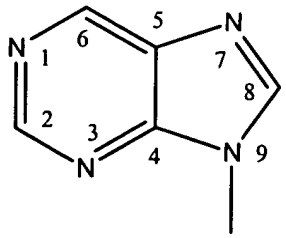
, (V)

wherein: V is H or N_3;

W is H or F; or

V and W together are a covalent bond; and

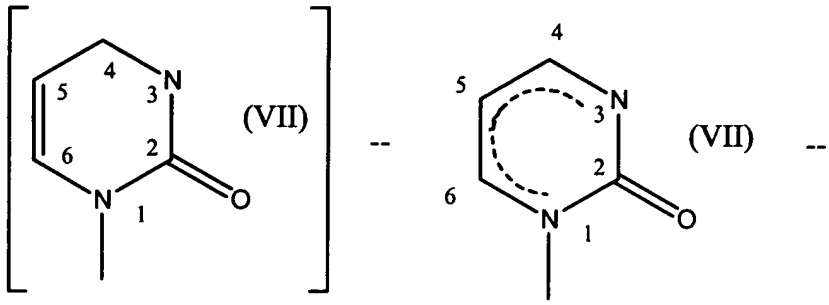
B is a purinyl moiety of Formula VI



(VI)

optionally substituted at position 2 with OH, -SH, $-NH_2$ or halogen, at position 6 with Cl, $-NH_2$, -OH, or C_1-C_3 alkyl, and at position 8 with Br or I; or

B is a pyrimidinyl moiety of Formula VII



substituted at position 4 with =O or NH_2 and optionally substituted at position 5 with halogen or C_1-C_3 saturated or unsaturated alkyl optionally substituted 1 to 3 times with halogen.